Efficacy of a paste formulation of omeprazole for the treatment of naturally occurring gastric ulcers in training standardbred racehorses in Canada

Michèle Y. Doucet, André A. Vrins, Rachel Dionne, Roberto Alva, Glenn Ericsson

Abstract — The efficacy of a paste formulation of the H^+, K^+, -ATPase inhibitor omeprazole was evaluated in standardbred racehorses for the treatment and prevention of gastric ulcers. Twenty standardbred racehorses in training, aged 2 to 9 years, were enrolled from 2 training centres in this field trial. Endoscopic examinations confirmed the presence of gastric ulcers in all horses, prior to allocation and treatment and on day 0. Lesions were scored on a scale of 0 to 3 (intact epithelium to extensive ulceration). Replicates were formed, based on training level and location. Within replicates, 1 horse was assigned to group 1 and 3 horses were assigned to group 2, randomly. Horses in group 1 were sham-dosed controls. Horses in group 2 were given omeprazole paste orally at 4 mg/kg bodyweight (BW)/day from day 0 to day 27 and 2 mg/kg BW/day of omeprazole paste orally from day 28 to day 57. Follow-up endoscopies were conducted on post treatment days 28 and 58 or 59. Physical examinations, including BWs, were conducted on all horses prior to treatment and on days 13 or 14, 28, 42 or 43, and 58 or 59. Horses treated with omeprazole had significantly ($P < 0.01$) more improvement in gastric lesion scores than did controls at day 28 and at study termination on days 58 or 59. All of the omeprazole-treated horses were improved relative to baseline ulcer score at both examinations, and 73.3% were healed (lesion score of 0) at both examinations. None of the controls improved at any point during the study. When the dose was reduced to 2 mg/kg BW, 80% of the horses showed no recurrences or worsening in gastric ulcers. It was concluded that omeprazole paste at 4 mg/kg BW orally, once daily is highly effective in healing gastric ulcers in standardbred racehorses in training and that a dose of 2 mg/kg BW orally, once daily, effectively prevents the recurrence of gastric ulcers in most horses.

Résumé — Efficacité d'une formulation d'oméprazole en pâte orale pour le traitement des ulcères gastriques d'origine naturelle chez les chevaux de course de race standardbred en entraînement au Canada. L'efficacité d'une formulation en pâte orale d'un l'inhibiteur de la pompe H^+, K^+ATPase, l'oméprazole, a été évaluée chez des chevaux de course de race standardbred pour le traitement et la prévention d'ulcères gastriques. Vingt chevaux standardbred à l'entraînement, âgés de 2 à 9 ans et provenant de 2 centres d'entraînement ont été inclus dans cette étude sur le terrain. Des examens endoscopiques ont confirmé la présence d'ulcères gastriques chez tous les chevaux avant de les assigner à un groupe de traitement au jour 0 de l'étude. Un score sur une échelle de 0 à 3 (épithélium intact à ulcération étendue) a été donné à chaque lésion. Les chevaux ont ensuite été répartis en échantillonnages de 4 chevaux selon le niveau d'entraînement et le site. Dans chaque échantillonnage, 1 cheval était assigné au hasard au groupe 1 et 3 chevaux au groupe 2. Les chevaux du groupe 1 étaient des contrôles traités avec une seringue vide tandis que les chevaux du groupe 2 recevaient la pâte orale d'oméprazole à raison de 4 mg/kg de poids corporel (PC) par jour du jour 0 au jour 27 puis 2 mg/kg PC par jour du jour 28 au jour 58 ou 59. Des examens endoscopiques de suivi ont été effectués aux jours 28 et 58 ou 59. Des examens physiques ainsi que la mesure du poids corporel, ont été effectués sur tous les chevaux avant le traitement ainsi qu'aux jours 13 ou 14, 28, 42 ou 43, et 58 ou 59. Une amélioration significative des scores des lésions gastriques au jour 28 et à la fin de l'étude au jour 58 ou 59 a été notée chez les chevaux traités avec l'oméprazole par rapport aux chevaux non-traités. Tous les chevaux traités avec l'oméprazole démontraient une amélioration des lésions par rapport au jour 0 aux deux évaluations et 73.3 % avaient des lésions guéries (score de lésion de 0) aux deux évaluations. Aucune lésion chez les chevaux du groupe contrôle ne s'est améliorée pour la durée de l'étude. Quand la dose a été diminuée à 2 mg/kg PC, 80 % des chevaux n'ont démontré aucune récurrence ou détérioration des ulcères gastriques. On peut conclure de cette étude que la pâte orale d'oméprazole à une dose de 4 mg/kg PC une fois par jour est très efficace pour

Département de biomédecine vétérinaire (Doucet) and Département de sciences cliniques (Vrins, Dionne), Faculté de médecine vétérinaire, Université de Montréal, CP 5000, Saint-Hyacinthe, Québec J2S 7C6; and Merial Limited, 3239 Satellite Blvd, Duluth, Georgia 30096-4640, USA (Alva, Ericsson).

Address all correspondence and reprint requests to Dre Michèle Doucet.

This study was supported by Merial Limited, Duluth, Georgia, USA.

la guérison des ulcères gastriques chez les chevaux standardbred à l'entraînement et qu'une dose de 2 mg/kg PC, une fois par jour, est efficace pour prévenir la récurrence des ulcères gastriques chez le plupart des chevaux.

(Traduction par Docteure Michèle Doucet)

Can Vet J 2003;44:581–585

Introduction

Gastric ulcers (GU) or equine gastric ulcer syndrome (EGUS) is highly prevalent in horses and may have an impact on condition and performance (1–3). The prevalence in Thoroughbred racehorses in training has been shown to be up to 90% (4–6). A recent study performed in Canada demonstrated that the prevalence in standardbred racehorses is 15.9% at rest, 28.3% in training, and 63.3% during racing (7); that is, slightly lower than in Thoroughbred horses. Equine gastric ulceration in yearlings and mature racehorses is commonly located in the nonglandular region of the stomach (6–8). Although the pathogenesis of the injury to the stratified squamous mucosa is still poorly understood and probably multifactorial, the predominant event is excessive exposure to hydrochloric acid (HCl) and pepsin (9). High intensity training and racing are closely associated with a high prevalence of gastric lesions in both Thoroughbred and standardbred racehorses (7,9). In standardbred racehorses, trotters were found to be twice more likely to develop GU than were pacers, and a significant association was found between poor body condition and lesions scores (7). These associations and risk factors have not been demonstrated in Thoroughbred racehorses.

Therapy is aimed at reducing gastric acidity in an attempt to provide an environment favorable for ulcer healing. During the last decade, various treatments to neutralize (antacids) or decrease (histamine H_2 receptor antagonists) the secretion of acid in the stomach have had mixed results in horses (10–15). Proton pump inhibitors constitute the most recent class of treatment for gastroduodenal disorders in humans. Omeprazole, a substituted benzimidazole, is a member of this class that blocks gastric acid secretion irrespective of stimulus (16). It decreases gastric acid secretion by blocking the H^+, K^+, ATPase (acid pump) in the secretory membrane of the parietal cell (17,18). This enzyme catalyses the exchange of hydrogen ions for potassium ions in the final step of hydrochloric acid production.

Omeprazole has been demonstrated to be a potent inhibitor of gastric acid secretion in horses (19–26) and, hence, should promote an environment in the equine stomach that is inducive to healing. Treatment of thoroughbred racehorses (27) and pleasure horses (28) with a "delayed release" formulation of omeprazole in capsules resulted in a more rapid and complete healing of naturally occurring gastric ulcers than did treatment with placebo (vehicle).

A paste formulation of omeprazole, developed for use in horses, significantly suppressed gastric acidity for up to 24 h when administered to horses at 4 mg/kg BW/d (25). This dose was also found to be effective in healing gastric ulcers, while a maintenance therapy of either 2 or 4 mg/kg BW/d effectively prevented gastric ulcer recurrence in Thoroughbred racehorses in training, compared with nontreated controls (29). To date, no field efficacy studies have been reported for the use of omeprazole in the treatment of naturally occurring GU in standardbred racehorses.

Given the observed differences in the prevalence, clinical signs, and risk factors associated with GU in standardbred racehorses compared with Thoroughbred racehorses, the purpose of this study was to verify the therapeutic efficacy of an oral omeprazole paste for treating naturally occurring gastric ulcers in standardbred racehorses in training and for preventing ulcer recurrence.

Materials and methods

Animals

Twenty standardbred racehorses in training from 2 training centers in Quebec were used in the study. They consisted of 13 geldings, 2 stallions, and 5 mares, 2 to 9 y of age, weighing 348 to 532 kg. All horses had a baseline gastric ulcer score of at least 1 but were otherwise considered healthy, based on a pretreatment physical examination. Horses were housed individually in stalls inside an environmentally controlled closed barn. Horses were fed a commercial ration according to standard practice for each location. Animals within the same replicate were exercised and managed similarly. None of the horses were allowed to race during the study; however, their training level was maintained as if they were racing on a regular basis.

Trial design and allocation

This double-blind study followed a randomized block design. Replicates of 4 horses were formed, based on training level and location. All horses within a replicate were located on the same farm and started treatment on the same day. One animal in each replicate was randomly assigned to receive sham treatment with an empty syringe and 3 animals were assigned to receive omeprazole paste (Gastrogard; Merial, Duluth, Georgia, USA). Study design is shown schematically in Figure 1.

Treatment

Each omeprazole paste syringe contained enough paste to administer omeprazole at 4 mg/kg BW to a horse weighing 575 kg. Treatments were administered, PO, q24h, in the morning prior to feeding, as follows: group 1: an empty syringe from day 0 to day 57; group 2: omeprazole at 4 mg/kg BW from day 0 to day 27 followed by 2 mg/kg BW from day 28 to day 57.

Gastroscopy

In order to confirm evidence of gastric ulcers (scores ≥ 1), endoscopic examination of the stomach mucosa was conducted on all horses prior to treatment by using a 3-m video endoscope (Model VSB-2900 video

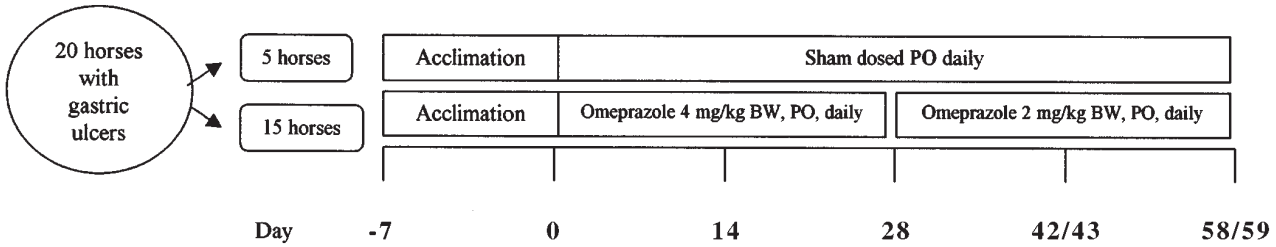

Figure 1. Schematic representation of study design. BW — body weight. PO — per os.

endoscope; Pentax, Mississauga, Ontario). Endoscopic examinations were conducted again on all horses, prior to treatment and on post treatment days 0, 28, and 58 or 59. The horses were fasted for 24 h prior to endoscopic examination. A twitch was applied, and the horse was restrained, either in stocks with tie chains or on a lead chain, and sedated if necessary and 100 mg xylazine (Rompun; Bayer, Etobicoke, Ontario) was administered, IV. After lubrication, the endoscope was passed through the nasal cavity and into the stomach. In order to see the mucosal surfaces, the stomach was distended and the surfaces were cleaned with an air and water pump. The gastroscopic examination included examination of the nonglandular portion of the stomach and approximately 90% of the glandular mucosa, the margo plicatus in the nonglandular portion of the stomach (fundus and larger curvature), the smaller curvature and cardia, and the glandular mucosa. The same researcher performed all endoscopic examinations and was blinded as to the treatment allocated to the animals.

Lesion scoring

For each horse, the endoscopist recorded a score for the worst stomach lesion in the nonglandular portion of the stomach. The following scoring system, based on that of Andrews et al (29), was used: 0, intact mucosal epithelium (can have reddening or hyperkeratosis); 1, small single or small multifocal lesion; 2, large single or large multifocal lesion; and 3, extensive (often coalescing) lesions with areas of apparent deep ulceration. The presence or absence of ulcers in the glandular portion of the stomach was also noted.

Animal monitoring

Beginning during acclimation (at least 7 d prior to start of trial) and continuing until day 58 or 59, horses were observed twice daily for health problems. The observer was blinded to the treatment allocated to the animals. Any health problems occurring during the trial were recorded. Each horse was given a complete physical examination and weighed once between day –8 and day 0, and again on days 13 or 14, 28, 42 or 43, and 58 or 59. The veterinarian performing the physical examination also was blinded to the treatment allocation of the animals.

Statistical analysis

The variables of interest were gastric lesion score and BW. Baseline gastric lesion score and change from baseline at days 28 and 58 or 59 were analyzed separately by time point using Wilcoxon's rank sum test (30). An exact 2-sided *P*-value was obtained for each analysis. Baseline BW and weight change to days 13 or 14, 28, 42 or 43, and 58 or 59 were analyzed by using randomized block analysis of variance, with replicate considered a random effect and treatment a fixed effect. Preliminary analysis indicated that the variability within replicates was similar in magnitude to the replicate by treatment interaction, so these 2 factors were pooled to obtain an estimate of residual variance. Significance was set at a level of 0.05 in all analyses.

Table 1. Frequency distribution of gastric lesion scores prior to treatment and on days 28 and 58 or 59 for sham-dosed control horses and the horses treated with omeprazole oral paste

		Gastric lesion scores				Two-sided
Day	Group	0	1	2	3	*P*-value
Pretreatment	Control	0	3	2	0	
0.0517						
Pretreatment	Treated	0	2	10	3	
28	Control	0	2	3	0	<
0.0001						
28	Treated	11	3	1	0	
58 or 59	Control	0	2	3	0	<
0.0001						
58 or 59	Treated	11	4	0	0	

Gastric lesion scores: 0: intact mucosal epithelium (can have reddening or hyperkeratosis); 1: small single or small multifocal lesion; 2: large single or large

Results

Only 2 horses required sedation with 100 mg xylazine, IV, during one endoscopy each. No health problems or side effects related to treatment were observed during the study. The paste was readily accepted by all of the omeprazole-treated horses. Horses in the control group gained an average of 15.6 kg, whereas treated horses gained an average of 10.8 kg from day 0 to day 58 or 59. There were no significant differences between groups with respect to weight gain.

The frequency distribution of gastric lesion scores in sham-dosed control horses and horses treated with omeprazole prior to treatment and on days 0, 28, and 58 or 59 are summarized in Table 1. All horses had pretreatment gastric lesion scores of at least 1. The pretreatment distribution of gastric lesion scores was not significantly different between the 2 treatment groups (Table 1). Gastric ulcers were healed in 11 of 15 (73.3%) omeprazole-treated horses on both days 28 and 58 or 59, whereas gastric ulcers were healed in 0 of 5 (0.0%) sham-dosed controls on these same days. Also, horses treated with omeprazole had significantly ($P < 0.01$)

Table 2. Change in gastric lesion scores from prior to treatment to day 28, between days 29 and, from prior to treatment to day 58 or 59 for the sham-dosed control group horses versus the horses treated

		Improved			No change	Worsened			Two-sided
Day	Group	-3	-2	-1	0	+1	+2	+3	*P*-value
Pretreatment to 28	Control	0	0	0	4	1	0	0	< 0.0001
Pretreatment to 28	Treated	2	7	6	0	0	0	0	
29 to 58 or 59	Control	0	0	0	5	0	0	0	
29 to 58 or 59	Treated	0	1	2	9	3	0	0	
Pretreatment to 58 or 59	Control	0	0	0	4	1	0	0	< 0.0001
Pretreatment to 58 or 59	Treated	2	8	5	0	0	0	0	

Gastric lesion scores: 0: intact mucosal epithelium (can have reddening or hyperkeratosis); 1: small single or small multifocal lesion; 2: large single or large multifocal lesion; and 3: extensive (often coalescing) lesions with areas of apparent deep ulceration

more improvement in gastric lesion scores than did controls at day 28 and at study termination. All of the omeprazole-treated horses were improved relative to their baseline ulcer score at both examinations. None of the controls improved at any point during the study (Table 2). Only 3 of the 15 (20%) treated horses had recurrence of gastric ulcers by day 58 or 59, whereas 3 of 15 (20%) horses continued to improve and the rest of the horses remained healed (8/15; 53%) or remained the same (1/15; 7%) when treated at 2 mg/kg BW of omeprazole (Table 2).

Discussion

The specially formulated omeprazole oral paste formulation for horses used in this study was found to be safe, easy to administer, and readily acceptable to all horses treated, in accordance with findings reported by Plue et al (31).

Healing rates observed in this study were similar to those reported previously with the same formulation and the same dose of omeprazole in Thoroughbred racehorses in training (29), where 77.3% of horses were healed at day 27. In a dose-titration study using horses with NSAID-induced gastric ulcers, omeprazole treatment resulted in a time- and dose-dependent positive effect with doses of 1, 2, and 4 mg/kg BW/d resulting in 45%, 56%, and 70% gastric ulcer healing after 28 d of treatment, respectively (32,33).

Healing and time-to-healing rates seen in the present study with omeprazole treatment are better than those reported elsewhere for histamine H_2 receptor antagonists in horses (10–14). In an uncontrolled retrospective study in adult horses, the healing rate for naturally occurring gastric ulcers was up to 84%, but healing required 4 wk of treatment with oral ranitidine at 6.6 mg/kg BW, q8h (12). However, in placebo-controlled studies using naturally occurring gastric ulcers, healing rates in ponies treated with ranitidine (4.4 mg/kg BW, PO, q8h) and cimetidine (12 and 18 mg/kg BW q8h) were no better than controls after 40 d of treatment (14,34). This difference in healing rates could be due to the difference in dose of ranitidine. Andrews et al (29) suggested that omeprazole was 5 times more potent, on an equimolar basis, than ranitidine in healing gastric ulcers in horses, and noted that omeprazole required once daily administration to effect this healing rate, whereas ranitidine required dosing 3 times a day. Pharmacologic studies have shown that omeprazole is rapidly transferred from plasma to the acidic secretory cannaliculi of the parietal cells (35) and covalently binds to the H^+, K^+, ATPase enzyme for the life of the parietal cells (36). Therefore, the antisecretory effects of omeprazole on parietal cells persists long after plasma concentrations have declined (37), allowing the drug to be administered only once daily. In contrast, the magnitude and duration of acid-inhibitory effects of the H_2 receptor antagonists are related to plasma concentrations and are short-lived (38). Results from the present study seem to support these comments and indicate that omeprazole treatment, in a specially formulated paste for horses, is a highly effective, acceptable, and easy to administer treatment for gastric ulcers in standardbred racehorses.

This trial also demonstrates that, after the initial healing (improvement from baseline) of gastric ulcers with omeprazole, a lower dose of omeprazole prevented recurrence or worsening during the subsequent 30-day period for 80% of the treated standardbred horses. A previous study in Thoroughbred horses in training (29) showed that omeprazole at either 2 or 4 mg/kg BW/d was effective as preventive therapy for gastric ulcers in horses in race training. The current study data support a similar conclusion for standardbred horses, despite the observed differences in risk factors for GU (7). Results also suggest that the healing process may continue in some horses despite the lower dose, since 3 of 15 treated horses had improved gastric lesion scores between days 29 and 58 or 59. Only 20% (3/15) of omeprazole-treated horses had recurrence of gastric ulcers, despite remaining in race training, and the gastric lesion scores in these horses on day 58 or 59 remained lower than the initial scores observed prior to treatment. In a similar study performed in Thoroughbred racehorses in training, a recurrence rate of 13% was observed when horses were treated with either 2 mg/kg BW or 4 mg/kg BW of omeprazole once daily for 30 d following an initial therapy at 4 mg/kg BW q24h for 28 d (29). In contrast, the same study showed that 90% of horses taken off omeprazole treatment after the initial 28 d of treatment had recurrence of gastric ulcers (29). This value corresponds to the high prevalence of gastric ulcers reported for Thoroughbred horses in training (2,5). Since management and training have been shown to be risk factors in causing and maintaining gastric ulcer disease in Thoroughbred horses (5,39) and that gate was also found to be a risk factor in standardbred horses (7),

high recurrence rates are probable once horses are taken off treatment while in training. Therefore, maintenance therapy may be necessary to prevent recurrence of gastric ulcer disease in these 2 breeds of racehorses. This finding is further supported by the fact that untreated horses in this study that remained in training for the duration of the trial, maintained and, in some cases, increased their gastric ulcer lesion scores during the trial period.

Acknowledgments

The authors thank Ms. Julie de Lasalle for her technical assistance, Ms. Jennifer Irwin for data auditing, and the horse owners and trainers involved with this trial.

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